WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/prequal/sites/default/files/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[HA479 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1g vial contains ceftriaxone sodium equivalent to 1g of ceftriaxone.

Each 1g vial contains 83 mg (3.6 mmol) sodium.

3. PHARMACEUTICAL FORM

Powder for solution for injection

White or yellowish crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[HA479 trade name], a broad-spectrum antibiotic, can be used in people with severe or advanced HIV disease to treat ceftriaxone-susceptible bacterial infections. Such infections include:

- Bacterial meningitis
- Community-acquired or hospital-acquired pneumonia
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

[HA479 trade name] may also be used:

- For treatment of acute exacerbation of chronic obstructive pulmonary disease in adults
- For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III))
- For pre-operative prophylaxis of surgical site infections
- In the management of neutropenic patients with fever and suspected bacterial infection
- For treatment of bacteraemia possibly associated with infections listed above

Regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines, including official guidance on the appropriate use of antibacterial agents and the treatment of opportunistic infections in HIV/AIDS patients.

4.2 Posology and method of administration

Treatment with [HA479 trade name] should be prescribed by a health care provider experienced in managing opportunistic infections in patients with HIV-1 infection.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Posology

Adults and adolescents older than 12 years and weighing at least 50 kg

Indication	Recommended dose	Treatment duration
Community-acquired pneumonia Acute exacerbations of chronic obstructive pulmonary disease Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis)	1 g once daily, increased in severe infection or in bacteraemia to 2 g once daily (or 1 g every 12 hours)	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Hospital-acquired pneumonia Complicated skin and soft tissue infections Infections of bones and joints	*Either* 2 g once daily *or* 1 g every 12 hours	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Neutropenia with fever suspected to be due to a bacterial infection Bacterial endocarditis Bacterial meningitis	*Either* 2 to 4 g once daily *or* 1 to 2 g every 12 hours; the higher dose is recommended for severe infection or bacteraemia	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Gonorrhoea	500 mg by intramuscular injection	Single dose
Syphilis	500 mg to 1 g once daily, increased to 2 g once daily for neurosyphilis	10 to 14 days
Disseminated Lyme borreliosis	2 g once daily	14 to 21 days
Pre-operative prophylaxis of surgical site infections	2 g	Single pre-operative dose

Neonates aged from 15 days to children 12 years of age and weighing less than 50 kg

The use of ceftriaxone in neonates is contraindicated in certain situations (see section 4.3).

Indication	Recommended dose	Treatment duration
Community-acquired pneumonia Hospital-acquired pneumonia Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis)	50 to 80 mg/kg once daily; the higher dose is recommended for severe infection or bacteraemia. Dose exceeding 2 g daily may be given in two equally divided doses 12 hours apart.	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Complicated skin and soft tissue infections Infections of bones and joints Neutropenia with fever suspected to be due to a bacterial infection	50 to 100 mg/kg once daily (maximum 4 g daily); the higher dose is recommended for severe infection or bacteraemia. Dose exceeding 2 g daily may be given in two equally divided doses 12 hours apart.	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated

Indication	Recommended dose	Treatment duration
Bacterial meningitis	80 to 100 mg/kg once daily (maximum 4 g daily); the higher dose is recommended for severe infection or bacteraemia. Dose exceeding 2 g daily may be given in two equally divided doses 12 hours apart.	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Bacterial endocarditis	100 mg/kg once daily (maximum 4 g daily). Dose exceeding 2 g daily may be given in two equally divided doses 12 hours apart.	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Syphilis	75 to 100 mg/kg once daily (maximum 4 g daily)	10 to 14 days
Disseminated Lyme borreliosis	50 to 80 mg/kg once daily	14 to 21 days
Pre-operative prophylaxis of surgical site infections	50 to 80 mg/kg	Single pre-operative dose

Neonates up to 14 days old

The use of ceftriaxone in neonates is contraindicated in certain situations (see section 4.3).

Indication	Recommended dose	Treatment duration
Community-acquired pneumonia Hospital-acquired pneumonia Intra-abdominal infections Complicated urinary tract infections (including pyelonephritis) Infections of bones and joints Complicated skin and soft tissue infections Neutropenia with fever suspected to be due to a bacterial infection	20 to 50 mg/kg once daily; the higher dose (up to 50 mg/kg) is recommended for severe infection or bacteraemia.	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Bacterial meningitis Bacterial endocarditis	50 mg/kg once daily	Usually continued for 2–3 days after the patient has been afebrile or the infecting bacteria have been eradicated
Syphilis	50 mg/kg once daily	10 to 14 days
Pre-operative prophylaxis of surgical site infections	20 to 50 mg/kg	Single pre-operative dose

Special populations

Elderly

No dose adjustment is required in the elderly.

Renal impairment

No dose adjustment is required in patients with renal impairment. In patients with end-stage renal disease (creatinine clearance less than 10 mL/minute), the ceftriaxone dose should not exceed 2 g daily.

Ceftriaxone is not removed by peritoneal dialysis- or haemodialysis.

Hepatic impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment.

There are no data in patients with severe hepatic impairment.

Patients with severe hepatic and renal impairment

In patients with both severe renal and hepatic dysfunction, the dose of [HA479 trade name] should not exceed 2 g daily and patients should be closely monitored for adverse effects and efficacy.

Method of administration

The intravenous route is generally preferred for administering [HA479 trade name], but it can be given by intramuscular injection.

Intramuscular injection

Ceftriaxone can be administered by deep intramuscular injection well into the bulk of a relatively large muscle. No more than 1 g should be injected at any one site.

The intramuscular injection can be prepared by dissolving ceftriaxone powder in lidocaine solution. The resulting solution must be given by intramuscular injection **only**.

Intravenous administration

Ceftriaxone can be administered by intravenous infusion over at least 30 minutes or by slow intravenous injection over 5 minutes preferably in larger veins.

Intravenous doses of 50 mg/kg or more in infants and children up to 12 years of age should be given by infusion. In neonates, intravenous doses should be infused over 60 minutes to reduce the risk of bilirubin encephalopathy. Intramuscular administration should only be considered when the intravenous route is not possible or is less appropriate for the patient. For doses greater than 2 g intravenous administration should be used.

Precipitation of ceftriaxone calcium can occur if ceftriaxone comes into contact with calcium-containing solutions.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

[HA479 trade name] is contraindicated in patients with:

- hypersensitivity to ceftriaxone, any other cephalosporin
- a history of severe hypersensitivity (e.g. anaphylactic reaction) to any other type of beta-lactam antibacterial agents (penicillins, monobactams, carbapenems)

[HA479 trade name] is contraindicated in:

- neonates at risk of bilirubin encephalopathy (because ceftriaxone can displace bilirubin from albumin binding sites):
  - preterm neonates whose combined gestational age and chronological age is less than 41 weeks
  - full-term neonates with impaired bilirubin binding because of hyperbilirubinaemia, hypoalbuminaemia or acidosis

- Full-term neonates who are receiving (or are expected to receive) intravenous therapy with calcium-containing solutions – risk of precipitation of a ceftriaxone-calcium salt (see also section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions have been reported for beta-lactam antibiotics, including ceftriaxone. Before starting treatment, a history of severe hypersensitivity reactions to ceftriaxone, to other cephalosporins or to any other beta-lactam agent should be ruled out. Ceftriaxone should be given with caution to patients with a history of non-severe hypersensitivity to other beta-lactams. In case a severe hypersensitivity reaction occurs, ceftriaxone should be stopped immediately and suitable emergency treatment started.

Severe cutaneous adverse reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis have been reported (see section 4.8). Patients should be advised to contact their health care provider immediately if signs and symptoms of such a reaction occur.

Interaction with calcium-containing products

Fatal reactions involving calcium-ceftriaxone precipitates in lungs and kidneys have occurred in preterm and full-term neonates aged less than 1 month. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. Such reactions have not been reported in patients other than neonates. In vitro studies demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups (see also section 4.8).

Ceftriaxone must not be mixed with, or given simultaneously with, a calcium-containing intravenous solution, even through different infusion lines or at different infusion sites. In patients older than 28 days, ceftriaxone and calcium-containing solutions may be given one after another at different sites or at the same site if infusion lines are replaced or thoroughly flushed with physiological salt-solution between infusions.

In patients requiring continuous calcium-containing total parenteral nutrition (TPN) solutions, an alternative antibacterial treatment, which does not carry a risk of precipitation, may be considered. If ceftriaxone is considered necessary, TPN solutions and ceftriaxone can be administered through different infusion lines and at different sites. Alternatively, TPN solution could be stopped during ceftriaxone infusion and the infusion lines flushed between solutions.

Immune-mediated haemolytic anaemia

Severe cases of immune-mediated haemolytic anaemia, including fatalities, have been reported during ceftriaxone treatment in adults and children.

If a patient develops anaemia while on ceftriaxone, the diagnosis of a cephalosporin-associated anaemia should be considered, and ceftriaxone discontinued until the aetiology is determined.

Long-term treatment

During prolonged treatment complete blood count should be performed at regular intervals.

Antibiotic-associated colitis and overgrowth of non-susceptible microorganisms

Diarrhoea, particularly if severe, persistent or bloody, during or after treatment with [HA479 trade name], may be a symptom of antibiotic-associated colitis, which can be life-threatening. Therefore, if antibiotic-associated colitis is suspected or confirmed, [HA479 trade name] must be stopped immediately, and diarrhoea should be appropriately managed without delay. Products inhibiting peristalsis are contraindicated in this situation.

Superinfection may occur with organisms not susceptible to ceftriaxone.

Severe renal and hepatic insufficiency

In patients with severe renal and hepatic insufficiency, close clinical monitoring for adverse reactions and efficacy is advised (see section 4.2).

Interference with tests

[HA479 trade name] may interfere give a false positive result with Coombs tests. It can also give a false-positive result for galactosaemia.

Non-enzymatic methods for glucose in urine may give false-positive results.

Sodium

[HA479 trade name] contains 83 mg sodium for 1 g of ceftriaxone. This should be taken into consideration in patients on a controlled sodium diet.

It is important to consider the contribution of excipients from all the medicines that the patient is taking

Biliary lithiasis

Precipitates of calcium ceftriaxone may show up as shadows on sonograms that could be mistaken for gallstones. Such sonogram shadows are more frequent with ceftriaxone doses of at least 1 g daily. Caution should be particularly used in children. Calcium ceftriaxone precipitates disappear after ceftriaxone therapy ends. Rarely, if the precipitates cause symptoms, conservative nonsurgical management is recommended; ceftriaxone may be discontinued if the patients' clinical condition allows this.

Biliary stasis

Pancreatitis, possibly caused by biliary obstruction, has been reported in patients treated with ceftriaxone. Most of these patients had higher risk for biliary stasis and biliary sludge e.g. because of preceding major therapy, severe illness and total parenteral nutrition. It is possible that ceftriaxone-related biliary precipitation contributed to the pancreatitis.

Renal lithiasis

Renal lithiasis has been reported, which is reversible on discontinuing ceftriaxone. In symptomatic cases, sonography should be used. Health care providers should consider whether or not to use ceftriaxone in patients with a history of renal lithiasis or with hypercalciuria, based on patient's clinical status.

4.5 Interaction with other medicinal products and other forms of interaction

Ceftriaxone may enhance the anticoagulant effects of concomitantly administered vitamin K antagonists such as warfarin and so increase the risk of bleeding. Frequent monitoring of the international normalised ratio (INR) is recommended and the dose of the anticoagulant adjusted accordingly, both during and after treatment with ceftriaxone.

There is conflicting evidence regarding a potential increase in renal toxicity of aminoglycosides when used with cephalosporins. The recommended monitoring of aminoglycoside levels (and renal function) in clinical practice should be closely adhered to in such cases.

A laboratory study found reduced antibacterial effect with the combination of chloramphenicol and ceftriaxone. The clinical relevance of this finding is unknown.

Interaction with calcium-containing products

Do not use calcium-containing diluents, such as Ringer's solution or Hartmann's solution to reconstitute ceftriaxone vials or to dilute a reconstituted vial for intravenous administration because a precipitate can form.

Precipitation of ceftriaxone calcium can also occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be administered simultaneously

with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition through a Y-site.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

Ceftriaxone crosses the placental barrier. There are limited data on the use of ceftriaxone in pregnant women. Animal studies do not indicate harmful effects on embryonic, fetal, perinatal and postnatal development (see section 5.3). Ceftriaxone should only be administered during pregnancy, and in particular in the first trimester of pregnancy, when the woman's clinical situation requires such treatment.

Breast-feeding

Ceftriaxone is present in human milk in low concentrations but it is not expected to affect the breast-feeding infant. However, there is a theoretical risk of diarrhoea and fungal infection of the mucous membranes in the infant. The possibility of sensitisation should also be considered.

When considering the use of ceftriaxone, the developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for treatment.

Fertility

Reproductive studies have not shown evidence of adverse effects on male or female fertility.

4.7 Effects on ability to drive and use machines

[HA479 trade name] is unlikely to affect the ability to drive or operate machinery.

However, patients should be advised to consider if their clinical status, including any undesirable effects of the medicine, allows them to perform skilled tasks safely.

4.8 Undesirable effects

The most frequently reported adverse effects of ceftriaxone are eosinophilia, leucopenia, thrombocytopenia, diarrhoea, rash, and increased hepatic enzymes.

Adverse reactions of ceftriaxone based on clinical trials and post-marketing data are listed below by body system or organ. Frequencies are defined as very common (at least 1 in 10), common (1 in 100 to 1 in 10), uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000), very rare (less than 1 in 10 000) or not known (frequency cannot be estimated from available data).

Infections and infestations

Uncommon	genital fungal infection
Rare	antibiotic-associated colitis (see also section 4.4)
Not known	superinfection

Blood and lymphatic disorders

Common	eosinophilia, leucopenia, thrombocytopenia
Uncommon	anaemia, coagulopathy, granulocytopenia
Not known	agranulocytosis, haemolytic anaemia (see also section 4.4)

Immune system disorders

Not known	anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, Jarisch-Herxheimer reaction

Nervous system disorders

Uncommon	dizziness, headache

Rare	encephalopathy
Very rare	convulsion

Ear and labyrinth disorders

Not known	Vertigo

Respiratory, thoracic and mediastinal disorders

Rare	bronchospasm

Gastrointestinal disorders

Common	diarrhoea (see also 'Infections and infestations', above), loose stools
Uncommon	nausea, vomiting
Not known	glossitis, pancreatitis (see also 'Biliary stasis' in section 4.4), stomatitis

Hepatobiliary disorders

Common	hepatic enzyme increased
Not known	precipitation in gallbladder, cholestatic hepatitis, hepatitis (see also 'Biliary lithiasis' in section 4.4), bilirubin encephalopathy

Skin and subcutaneous tissue disorders

Common	rash
Uncommon	Pruritus
Rare	urticaria
Not known	acute generalised exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

Renal and urinary disorders

Rare	glycosuria, haematuria
Unknown	oliguria, precipitation in kidneys

General disorders and administration site conditions

Uncommon	injection site reactions (including pain, erythema, swelling, rash, pruritus and induration), phlebitis, pyrexia
Rare	chills, oedema

Investigations

Uncommon	blood creatinine increased
Not known	false positive Coombs test, false positive galactosaemia test, false positive non-enzymatic methods for glucose determination (see also section 4.4)

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (aged under 28 days) who had been treated with intravenous ceftriaxone and calcium. Ceftriaxone calcium precipitates have been observed in lungs and kidneys post-mortem. The high risk of precipitation in neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see also sections 4.4, and 5.2).

Cases of ceftriaxone precipitation in the urinary tract have been reported, mostly in children treated with high doses (e.g. at least 80 mg/kg daily or total doses exceeding 10 g) and who have other risk factors (e.g. dehydration, confinement to bed). Ceftriaxone precipitation may be asymptomatic or symptomatic and may

lead to ureteric obstruction and postrenal acute renal failure, but is usually reversible on discontinuing ceftriaxone.

Ceftriaxone calcium salt precipitation in the gallbladder can occur, primarily in patients treated with doses exceeding the recommended standard dose. In children, studies have shown a variable incidence of precipitation with intravenous use – above 30% in some studies. The incidence appears to be lower with slow infusion (20–30 minutes). This effect is usually asymptomatic, but, rarely, precipitations has been accompanied by symptoms such as pain, nausea and vomiting. Symptomatic treatment is recommended in these cases. Precipitation is usually reversible upon discontinuing ceftriaxone.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Overdoses can result in nausea, vomiting and diarrhoea.

Treatment of overdose should consist of general supportive measures including monitoring the patient's clinical status. Ceftriaxone concentrations cannot be reduced by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, third-generation cephalosporins, ATC code: J01DD04

Mechanism of action

Ceftriaxone inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

It has activity against a range of Gram-positive and Gram-negative pathogens, also in the presence of some beta-lactamases (both penicillinases and cephalosporinases).

Mechanism of resistance

Bacterial resistance to ceftriaxone may be due to one or more of the following mechanisms:

- hydrolysis by beta-lactamases, including extended-spectrum beta-lactamases (ESBLs), carbapenemases and Amp C enzymes that may be induced or stably derepressed in certain aerobic Gram-negative bacterial species.
- reduced affinity of penicillin-binding proteins for ceftriaxone. As a result, all meticillin-resistant staphylococci are resistant to ceftriaxone
- outer membrane impermeability in Gram-negative organisms
- bacterial efflux pumps

Antibacterial spectrum

Inherently resistant organisms

Ceftriaxone should **not** be used to treat infections likely to be caused by the following organisms:

Gram-positive aerobes:	*Enterococcus* spp., *Listeria monocytogenes*
Gram-negative aerobes:	*Acinetobacter baumannii, Pseudomonas aeruginosa, Stenotrophomonas maltophilia*
Anaerobes:	*Clostridium difficile*

Others: *Chlamydia* spp., *Chlamydophila* spp., *Mycoplasma* spp., *Legionella* spp., *Ureaplasma urealyticum*

Organisms for which acquired resistance may be a problem

Susceptibility testing is advised when treating infections likely to be caused by the organisms listed below that may acquire resistance. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

Gram-positive aerobes: *Staphylococcus epidermidis, S. haemolyticus, S. hominis*

Gram-negative aerobes: *Citrobacter freundii, Enterobacter aerogenes, E. cloacae, Escherichia coli, Klebsiella pneumoniae, K. oxytoca, Morganella morganii, Proteus vulgaris, Serratia marcescens*

Anaerobes: *Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp., *Clostridium perfringens*

5.2 Pharmacokinetic properties

Pharmacokinetics of ceftriaxone

<table>
<tr><th></th><th>Ceftriaxone</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Absorption</td><td>
<table>
<tr><th>Dose</th><th>500 mg</th><th>1 g</th><th>2g</th></tr>
<tr><td colspan="4">Intravenous injection</td></tr>
<tr><td>C_{max}</td><td>120 mg/L</td><td>200 mg/L</td><td></td></tr>
<tr><td colspan="4">Intravenous infusion</td></tr>
<tr><td>C_{max}</td><td>80 mg/L</td><td>150 mg/L</td><td>250 mg/L</td></tr>
<tr><td colspan="4">Intramuscular injection</td></tr>
<tr><td>C_{max}</td><td></td><td>81</td><td></td></tr>
</table>
C_{max} is increased by about 8−15 % following repeated administration.

Steady-state within 48−72 hours depending on the route of administration.</td></tr>
<tr><td>Intramuscular injection</td><td>Mean peak plasma ceftriaxone levels are about half those after intravenous administration of an equivalent dose and are reached 2−3 hours after administration.

Area under the plasma concentration-time curve equivalent to that after intravenous administration of an equivalent dose.</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>General</td><td>Concentrations well above the minimal inhibitory concentrations (MIC) of most relevant pathogens are detectable in lung, heart, biliary tract, liver, tonsils, middle ear and nasal mucosa, bone, and in cerebrospinal, pleural, prostatic and synovial fluids.

Mean peak ceftriaxone concentrations in CSF: up to 25% of plasma levels in patients with bacterial meningitis; 2% of plasma levels in patients with uninflamed meninges.

Ceftriaxone crosses the placenta and present in breast milk at low concentration.

Peak concentrations in CSF approximately 4−6 hours after dosing</td></tr>
<tr><td>Volume of distribution at steady state (mean)</td><td>Approximately 7–12 L/kg</td></tr>
</table>

Plasma protein binding	Reversibly bound to albumin. About 95% at plasma concentrations below 100 mg/L. Binding is saturable and the bound portion decreases with increasing concentration (up to 85% at a plasma concentration of 300 mg/L).
Metabolism	
	Not metabolised systemically, but converted to inactive metabolites by the gut flora.
Active metabolites	None
Elimination	
Elimination half life	Approximately 8 hours
Mean systemic clearance (Cl/F)	10–22 mL/minute (total ceftriaxone) Renal clearance about 5–12 mL/minute
% of dose excreted in urine	50–60% unchanged ceftriaxone, primarily by glomerular filtration
% of dose excreted in bile	40–50% unchanged ceftriaxone
Pharmacokinetic linearity	Non-linear for total plasma ceftriaxone due to saturation of plasma protein binding. All basic pharmacokinetic parameters, except the elimination half-life, are dose dependent if based on total drug concentrations, increasing less than proportionally with dose.

Special populations

Renal or hepatic impairment

In patients with renal or hepatic dysfunction, the pharmacokinetics of ceftriaxone are only minimally altered with slightly increased half-life (less than 2-fold), even in patients with severely impaired renal function.

Elderly

In people aged over 75 years, the average elimination half-life is usually 2–3 times that of young adults.

Paediatric patients

The half-life of ceftriaxone is prolonged in neonates. From birth to 14 days of age, the levels of free ceftriaxone may be further increased by factors such as reduced glomerular filtration and altered protein binding. In children, the half-life is shorter than in neonates or in adults.

The plasma clearance and volume of distribution of total ceftriaxone are greater in neonates, infants and children than in adults.

5.3 Preclinical safety data

In animal studies, high doses of ceftriaxone calcium salt led to formation of concrements and precipitates in the gallbladder of dogs and monkeys, which was reversible.

Animal studies produced no evidence of toxicity to reproduction and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients

6.2 Incompatibilities

Solutions containing ceftriaxone should not be mixed with or added to other agents except those mentioned in section 6.6.

Diluents containing calcium, (e.g. Ringer's solution, Hartmann's solution) should not be used to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration as a precipitate can form. Ceftriaxone must not be mixed or administered simultaneously with calcium containing solutions including total parenteral nutrition (see section 4.2, 4.3, 4.4 and 4.8).

6.3 Shelf life

36 months

In-use, chemically and physically

The use of freshly prepared solutions is recommended. These maintain potency for at least 6 hours at or below 25°C in daylight, or 24 hours at refrigerator at 2°C -8°C.

For shelf life of diluted product see section 6.6

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Single use vials. The product should be used immediately Discard any unused portion.

6.5 Nature and contents of container

Glass vial

Type II glass vials with grey bromobutyl stoppers covered with aluminium pilfer-proof caps.

Ceftriaxone (as sodium) 1g vial for injection is available in packs of 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for Reconstitution

The content of the vials must be reconstituted before administration to the patient. The volume of diluent to be used for the reconstitution depends on the method of administration.

The reconstituted solution is a clear solution with a yellow to brown-yellow colour.

It is recommended that reconstituted solutions are freshly prepared and any unused solution discarded. However, if necessary, reconstituted solutions may be stored for a limited period - see conditions for storage in section 6.3.

Intravenous injection or infusion

The infusion line should be flushed after each dose.

Reconstitution

1 g {DotWP-ProductName} should be reconstituted with 10 mL water for injections to produce a solution containing ceftriaxone 100 mg/mL. No other solutions should be used for reconstitution.

The vial should be gently rolled between the palms for dissolution and inspected to ensure that no particles remain undissolved.

The correct dose of the reconstituted solution can be administered over 5 minutes either directly into a vein or into the tubing of an intravenous infusion.

The reconstituted solution should be diluted further to produce a solution containing 50 mg/mL for intravenous infusion.

Dilution for intravenous infusion

For intravenous infusion, the reconstituted solution should be diluted further with 2 mL of one of the following calcium-free infusion solutions:

sodium chloride 0.9%

sodium chloride 0.45% and glucose 2.5%

glucose 5% or 10%

dextran 6% in glucose 5%,

water for injections

Intramuscular injection

Reconstitution

Because intramuscular injection of ceftriaxone is painful, 1% lidocaine hydrochloride solution can be used for reconstitution instead of water for injections. No other solutions should be used for reconstitution.

1 g {DotWP-ProductName} should be reconstituted with 3.5 mL of 1% lidocaine hydrochloride injection.

The vial should be gently rolled between the palms for dissolution and inspected to ensure that no particles remain undissolved.

The correct dose of the reconstituted solution should be given by deep intramuscular injection. Doses exceeding 1 g should be divided and given over 2 or more sites. Different sites should be selected for subsequent doses; successive intramuscular injections should not be given at the same site.

7. SUPPLIER

Egyptian International Pharmaceutical Industries Co. (EIPICO)
Tenth of Ramadan City
Industrial Area B1
Egypt

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

HA479

9. DATE OF PREQUALIFICATION

16 May 2014

10. DATE OF REVISION OF THE TEXT

March 2025

References

Rocephin 1 g Powder for solution for injection or infusion: summary of product characteristics. MHRA; 6 February 2024 (https://mhraproducts4853.blob.core.windows.net/docs/5643a8b9076811c9f3958e536d46fe76e192b57d , accessed 21 June 2024)

Ceftriaxone for injection (Sandoz): labelling. U.S. Food and Drug Administration; February 2014 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/065169s022lbl.pdf, accessed 21 June 2024)

Rocephin – referral (EMEA/H/A-30/1302) - Annex III. European Medicines Agency; 21 March 2014 (https://www.ema.europa.eu/en/documents/referral/rocephin-article-30-referral-annex-iii_en.pdf, accessed 21 June 2024)

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products